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NEW RESEARCH

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The Association of Paternal IQ With Autism Spectrum Disorders and Its Comorbidities: A Population-Based Cohort Study

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Objective: Original case descriptions of autism noted that parents of the affected children tended to be highly educated and intelligent, a characterization that has endured publicly. Recent genetic studies indicate that risk for autism spectrum disorders (ASD) is associated with high intelligence. We examined the association between paternal intelligence and ASD, considering co-occurring intellectual disability (ID) and attention-deficit/hyperactivity disorder (ADHD).

Method: We used a register-based cohort study design including 360,151 individuals with fathers conscripted to the Swedish military, resident in Stockholm, Sweden, born from 1984 to 2008, and followed until December 31, 2011, for diagnosis of ASD, ADHD, and/or ID. Risk of neurodevelopmental disorders relative to paternal IQ (rated on a 9-point scale) was assessed using a score of 5 (average intelligence) as the referent in models accounting for potentially nonlinear relationships and clustering of siblings.

Results: We observed an association between high paternal IQ and offspring risk of ASD without ID/ADHD in models adjusted for individual and family characteristics ($OR_{IQ=9}$ 1.32, 95% CI 1.15−1.52), an association that appeared to be driven largely by the fathers' score on the technical comprehension portion of the test ($OR_{Technical\ IQ\ =\ 9}$ 1.53, 95% CI 1.31−1.78). Conversely, low paternal IQ was associated with ASD+ID ($OR_{IQ\ =\ 1}$1.78, 95% CI 1.27−2.49) and ASD+ADHD ($OR_{IQ\ =\ 1}$1.40, 95% CI 1.16−1.70); low paternal IQ was strongly associated with ID ($OR_{IQ\ =\ 1}$ 4.46, 95% CI 3.62−5.49) and present also for ADHD ($OR_{IQ\ =\ 1}$1.56, 95% CI 1.42−1.72)] without co-occurring ASD or ID.

Conclusion: The relationship between paternal IQ and offspring risk of ASD was nonmonotonic and varied by the presence of co-occurring disorders, probably reflecting phenotypic diversity among affected individuals.

Key words: autism spectrum disorders, attention-deficit/hyperactivity disorder, intellectual disability, cognitive abilities

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Original descriptions of what are today considered autism spectrum disorders (ASD) noted impaired social interactions, restricted interests, and repetitive behaviors in children with a wide range of intellectual abilities, including special skills regarding numeracy and memory even in the presence of other learning difficulties.[1,2] Many of the parents of autistic children were described as highly educated and apparently highly intelligent.[1-3] Subsequent studies have observed an association between STEM (Science, Technology, Engineering, and Math) careers among parents and ASD in children.[4-6] However, population-based studies from countries with universal health care report higher ASD prevalence among lower socioeconomic status (SES) families,[7] raising the question of whether previously reported associations were due to greater access to care.[5] Nevertheless, recent studies show that common genetic variation associated with ASD is also associated with higher cognitive abilities,[8-13] in apparent support of the first clinical observations.

Existing studies, reviewed recently by Crespi,[14] regarding the cognitive abilities of first-degree relatives (parents or siblings) of individuals affected by ASD have been equivocal because of issues of power and selection biases.[15-18] One potential difficulty in characterizing the cognitive abilities of relatives of individuals affected by ASD is the phenotypic heterogeneity observed among those with ASD. Comorbidities common to ASD, such as intellectual disability (ID) and attention-deficit/hyperactivity disorder (ADHD), are themselves associated with heritable impairments of cognitive functions. Although risk for both ASD and severe ID has been associated with de novo variants,[19] family studies suggest that most cases of mild ID (IQ =

50–69) are explained by the same genetic and environmental factors responsible for the distribution of IQ in the general population.[20,21] In contrast, individuals affected by ASD and co-occurring ID have inherited on average more alleles positively associated with cognitive abilities than their unaffected siblings.[22] This raises the question of whether the etiology of ID among individuals affected by ASD is different from ID in individuals not affected by ASD.

We performed a systematic study of the association between IQ, assessed in men by the Swedish military during conscription, and subsequent risk of ASD, ADHD, ID, or co-occurring combinations of these disorders in their offspring. We also examined whether these relationships vary across the cognitive domains assessed at the time of conscription or by the severity of disability, in the case of ID.

METHOD

Study Population

We defined a prospective, register-based cohort of individuals born from 1984 to 2008 and resident in Stockholm County for ≥3 years, nested within the previously described Stockholm Youth Cohort.[23] Outcome and covariate data were extracted from national and regional data registers containing routinely collected health and sociodemographic data crosslinked via each resident's unique national identification number.[24]

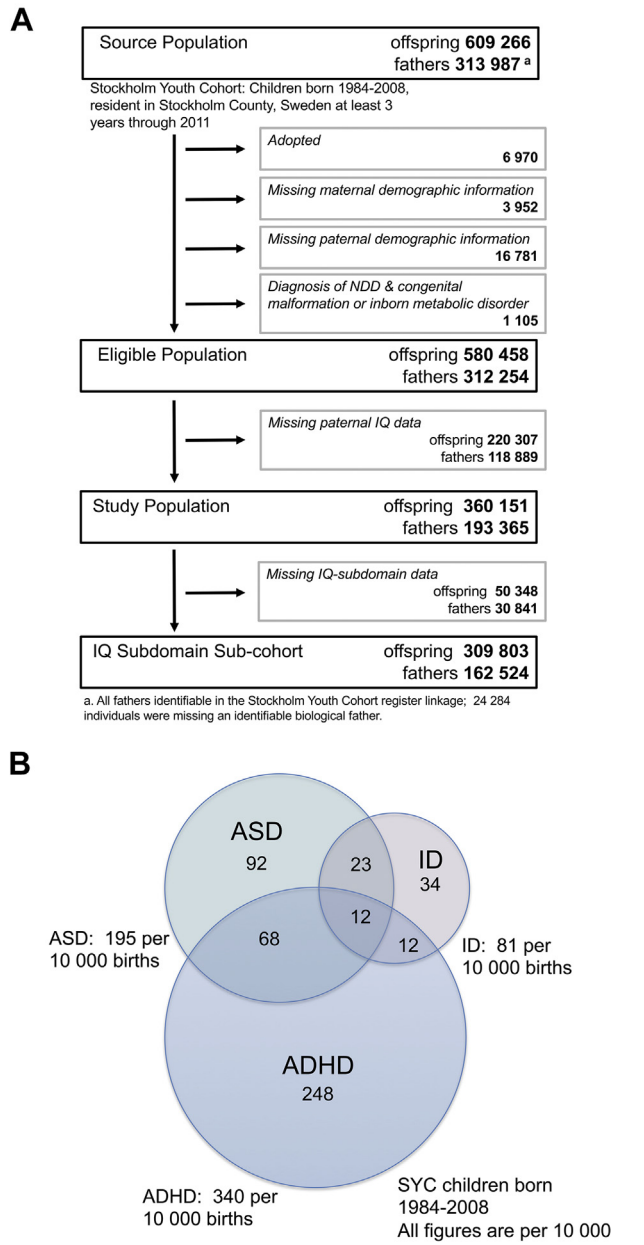
Individuals who were adopted or were missing complete demographic data were excluded from the study (Figure 1). We also excluded those individuals affected by a study outcome who were also affected by a congenital disorder known to be associated with ID (eg, Down syndrome) (Table S1, available online).

This study was approved by the regional ethical review board for Karolinska Institutet. Informed consent was not required for the analysis of anonymized register data.

Outcomes

Outcomes were ascertained using diagnoses taken from national and regional health care registers documenting health care services received by individuals within the source population (Figure 1). Diagnostic outcomes as of December 31, 2011, were defined by validated procedures covering all inpatient and outpatient pathways to care and diagnosis in Stockholm County (Table S2, available online).[23,25-27] We have considered the seven mutually exclusive diagnostic outcomes resulting from all possible combinations of ASD, ADHD, and ID (Figure 1, Table 1). We also considered the three overlapping diagnostic groups (regardless of co-occurring diagnoses): individuals who received any diagnosis of ASD, any diagnosis of ADHD, or any diagnosis of ID. For example, a person diagnosed with ASD and ID would be considered in both the "Any ASD" and "Any ID" diagnostic groups. We classified individuals diagnosed with

FIGURE 1 Sample Selection and Diagnostic Overlap in the Stockholm Youth Cohort



Note: (A) Derivation of the analytical sample from the Stockholm Youth Cohort. From the original source population, children with a registered diagnosis of a neurodevelopmental disorder (ie, autism spectrum disorder [ASD], attention-deficit/hyperactivity disorder [ADHD], and/or intellectual disability [ID]) as well as a registered diagnosis of a congenital malformation or inborn metabolic disorder (see Table S1, available online) were excluded. (B) Prevalence and overlap of diagnoses for three different neurodevelopmental disorders among the 360,803 children included in the study population. NDD = neurodevelopmental disorders; SYC = Stockholm Youth Cohort. Please note color figures are available online.

TABLE 1 Characteristics of the Stockholm Youth Cohort, Born 1984-2008, According to Paternal IQ Score

	Paternal IQ																	
	1 (IQ<74)		2 (74 ≥ IQ ≤ 81)		3 (82 ≥ IQ ≤ 89)		4 (90 ≥ IQ ≤ 95)		5 (96 ≥ IQ ≤ 104)		6 (105 ≥ IQ ≤ 110)		7 (111 ≥ IQ ≤ 118)		8 (119 ≥ IQ ≤ 126)		9 (IQ>126)		Total	
	n = 7,908		n = 16,720		n = 27,913		n = 44,131		n = 74,572		n = 66,929		n = 57,664		n = 39,994		n = 24,320		N = 360,151	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Offspring Diagnosis																				
ASD only	81	1.02	181	1.08	260	0.93	381	0.86	659	0.88	569	0.85	547	0.95	364	0.91	263	1.08	3,305	0.92
ID only	119	1.50	150	0.90	178	0.64	137	0.31	231	0.31	177	0.26	113	0.20	90	0.23	27	0.11	1,222	0.34
ADHD only	425	5.37	791	4.73	1,056	3.78	1,460	3.31	2,014	2.70	1,361	2.03	926	1.61	592	1.48	298	1.23	8,923	2.48
ASD + ID	32	0.40	53	0.32	69	0.25	94	0.21	161	0.22	142	0.21	120	0.21	85	0.21	61	0.25	817	0.23
ASD + ADHD	96	1.21	176	1.05	241	0.86	340	0.77	497	0.67	394	0.59	341	0.59	225	0.56	123	0.51	2,433	0.68
ID + ADHD	56	0.71	68	0.41	76	0.27	74	0.17	66	0.09	46	0.07	31	0.05	16	0.04	7	0.03	440	0.12
ASD + ADHD + ID	24	0.30	42	0.25	57	0.20	58	0.13	87	0.12	62	0.09	55	0.10	31	0.08	22	0.09	438	0.12
ASD or ID or ADHD	833	10.51	1461	8.74	1937	6.93	2544	5.76	3715	4.99	2751	4.10	2133	3.71	1403	3.51	801	3.30	17578	4.89
In Highest Income Quintile																				
	412	5.21	1,346	8.05	3,119	11.17	6,929	15.70	16,164	21.68	19,145	28.60	20,079	34.82	15,701	39.26	10,506	43.20	93,401	25.93
12+ yr Completed Education																				
Mother	958	12.19	2,705	16.22	5,853	20.99	12,131	27.54	27,499	36.93	32,256	48.25	33,493	58.16	26,689	66.88	18,129	74.62	159,713	44.42
Father	304	3.85	851	5.11	2,466	8.86	7,207	16.37	22,651	30.44	32,573	48.74	37,620	65.31	31,143	77.94	20,764	85.47	155,579	43.27
Mother Born in Sweden																				
	5,448	68.89	14,023	83.87	24,428	87.51	39,467	89.43	67,199	90.11	60,630	90.59	52,088	90.33	35,881	89.72	21,748	89.42	320,912	89.10
Inpatient Psychiatric Care																				
Mother	977	12.35	1,822	10.90	2,561	9.17	3,548	8.04	5,047	6.77	4,005	5.98	3,142	5.45	2,006	5.02	1,134	4.66	24,242	6.73
Father	1,184	14.97	2,095	12.53	2,867	10.27	3,740	8.47	4,329	5.81	3,177	4.75	2,105	3.65	1,295	3.24	575	2.36	21,367	5.93
Any Psychiatric Treatment																				
Mother	3,401	43.01	6,696	40.05	10,344	37.06	15,430	34.96	23,977	32.15	20,065	29.98	16,372	28.39	10,487	26.22	6,394	26.29	113,166	31.42
Father	2,624	33.18	4,869	29.12	7,193	25.77	10,302	23.34	14,237	19.09	11,195	16.73	8,607	14.93	5,340	13.35	2,971	12.22	67,338	18.70
Parental Age at Birth, Median (IQR)																				
Mother	26 (23–30)		27 (24–31)		28 (24–32)		29 (25–32)		30 (26–33)		30 (27–33)		31 (28–34)		31 (29–34)		32 (29–35)		30 (27–33)	
Father	29 (25–33)		29 (26–33)		30 (26–34)		30 (27–34)		31 (28–35)		32 (29–36)		33 (30–36)		33 (30–36)		33 (31–37)		32 (28–35)	

Note: Paternal IQ shown on the stanine (standardized nine point) scale, followed by approximate corresponding values on the quotient scale (with mean = 100, SD = 15). ADHD = attention-deficit/hyperactivity disorder; ASD = autism spectrum disorders; ID = intellectual disability; IQR = interquartile range.

ID by severity where possible, using the clinical categories of mild (IQ = 50−69), moderate (35−49), and severe or profound (<35) ID.

Assessment of Paternal IQ

Cognitive ability was measured at conscription with the Swedish Enlistment Battery (SEB) consisting of four tests: logic, verbal comprehension, spatial ability, and technical comprehension (Supplement 1, available online).[28-30] Scores on these tests were standardized and expressed on a nine-point (stanine) scale (Table 1).

Covariates

We considered as potential confounders covariates the distribution of which varied by level of paternal IQ (Table 1) and that were related to risk of any of the outcomes (Figure S1, available online). We also considered two characteristics (sex and birth order) of the index children that were predictors of any of the outcomes (Figure S1, available online). Quintiles of income were created by birth year of the child using the nationwide distribution, accounting for all sources of income and adjusting for family size.[7] Parental educational attainment (highest of mother or father) was categorized as ≤9 years, 10 to 12 years, or >12 years.[7] Maternal migrant status was categorized as born in Sweden or not, birth order as firstborn or not, and parental history of psychiatric inpatient treatment prior to the birth of the index child as no, one, or two parents with inpatient psychiatric history. Birth year, maternal age, and paternal age were centered and included in models as quadratic terms, to accommodate potentially nonlinear relationships with risk of neurodevelopmental outcomes.

Statistical Analyses

For our primary analysis, we used restricted cubic spline models with five knots followed by *xbrcspline* post-estimation[31] to flexibly fit the potentially nonlinear relationship between the paternal IQ score at conscription and offspring's likelihood of receiving any of the diagnostic outcomes. Each outcome was modeled separately. A score of 5 (average intelligence) was chosen as the referent. We used general estimating equation models with logit link clustered on family identification number to provide robust standard errors, accounting for fathers who contributed more than one child to the cohort. An unadjusted model was compared to a fully adjusted model, including children's characteristics (sex, birth year, birth order) and family characteristics (maternal age, paternal age, highest parental education level, family income quintile, maternal migration status, and parental inpatient psychiatric history) associated with the outcomes (Figure S1, available online). To examine the modulating effect of any individual covariate, we also examined the relationship between paternal IQ and the outcomes, adjusting for each potential confounder individually, and compared these results to the unadjusted and fully adjusted model estimates. To formally test whether paternal IQ in general was associated with each outcome (regardless of the shape of the association), we used Stata's testparm command to test the null hypothesis that all spline terms were equal to zero using the fully adjusted model estimates. Results for the null hypothesis test for association are given as $p_{\text{association}}$. Restricted cubic spline models allow for potentially nonlinear relationships between predictors and outcomes, although not all relationships that we considered are necessarily nonlinear. To formally assess evidence for nonlinear relationships between paternal IQ and each outcome, we tested the null hypothesis that all spline terms excluding the first spline term are equal to zero (ie, all spline terms that would indicate a change in direction or slope of the relationship are equal to zero). Results for the linearity null hypothesis test are given as $p_{\text{linearity}}$.

The primary analyses were repeated considering the paternal scores on the individual tests of the SEB. The study population was stratified on the sex of the offspring, and the above analyses were repeated.

We examined the relationship between paternal IQ and offspring risk of ID, stratified by severity, using the same modeling strategy. We combined the moderate and severe/profound outcomes into a single group (IQ < 50) to increase statistical power, and further stratified these ID outcome groups by the presence of co-occurring ASD.

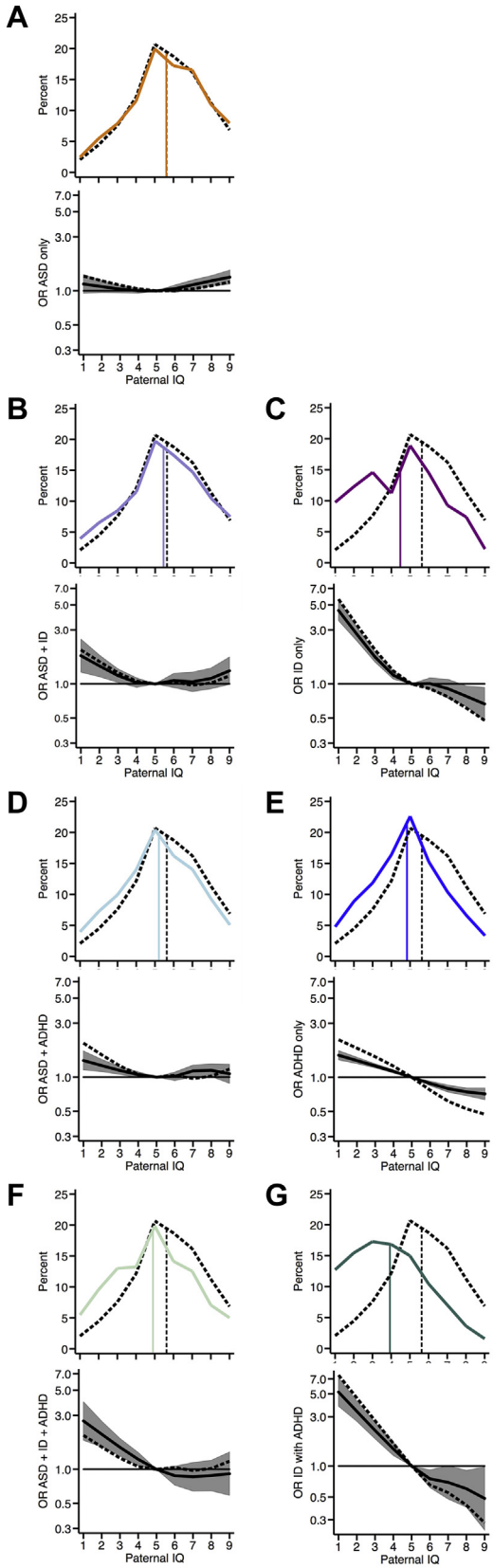
RESULTS

The proportion of individuals receiving any of the outcome diagnoses decreased with increasing paternal IQ, with 10.51% of fathers at the lowest IQ stratum having a child with one of the diagnostic outcomes (Table 1). Missingness of paternal IQ data varied somewhat by diagnostic group (Table S3, available online), largely explained by the proportion of fathers born outside of Sweden and thus not subjected to conscription. The distribution of the cognitive testing scores for the Stockholm-area men in our study was slightly right-skewed, with a mean of 5.60 (compared to the standardized national mean of 5.00).

Paternal IQ and Offspring Risk of Neurodevelopmental Disorders

Although the distribution of paternal IQ values was similar among fathers of children affected by ASD without ID/ADHD (mean = 5.62) and fathers of unaffected children (mean = 5.63), we observed a weak J-shaped relationship between paternal IQ and risk of ASD (adjusted OR_{IQ} =

FIGURE 2 Relationship Between Paternal IQ and Offspring Risk of Neurodevelopmental Disorders



$_{1}$1.15, 95% CI 0.95−1.39; $aOR_{IQ\ =\ 9}$ 1.32, 95% CI 1.15−1.52; $p_{association}$< .001; $p_{nonlinearity}$ = .007) (Figure 2A).

The distribution of paternal IQ scores observed among fathers of children diagnosed with ASD+ID (mean = 5.44) was shifted slightly lower compared to fathers of unaffected children, resulting in increased risk of ASD+ID associated with lower paternal IQ scores ($aOR_{IQ\ =\ 1}$1.78, 95% CI 1.27−2.49; $aOR_{IQ\ =\ 9}$ 1.31, 95% CI 0.99−1.73); $p_{association}$ = .008; $p_{nonlinearity}$ = .006) (Figure 2B). In contrast, the distribution of IQ scores for fathers of children affected by ID without ASD/ADHD was notably left-shifted (mean = 4.48). This resulted in a substantially increased risk of ID associated with lower paternal IQ, but only a moderately decreased risk at higher paternal IQ levels ($aOR_{IQ\ =\ 1}$ 4.46, 95% CI 3.62−5.49; $aOR_{IQ\ =\ 9}$ 0.66, 95% CI 0.48−0.93; $p_{association}$ < .001; $p_{nonlinearity}$ < .001) (Figure 2C).

The distribution of paternal IQ scores was shifted slightly lower for fathers of children diagnosed with ASD+ADHD (mean = 5.21), resulting in increased risk of ASD+ADHD associated with lower paternal IQ scores ($aOR_{IQ\ =\ 1}$1.40, 95% CI 1.16−1.70; $aOR_{IQ\ =\ 9}$ 1.07, 95% CI 0.88−1.29; $p_{association}$ = .002; $p_{nonlinearityc}$ = .002) (Figure 2D). The distribution of IQ scores for fathers of children affected by ADHD without ASD/ID was more notably shifted toward lower values (mean = 4.84). Paternal IQ was inversely associated with offspring risk of ADHD in a monotonic fashion ($aOR_{IQ\ =\ 1}$1.56, 95% CI 1.42−1.72; $aOR_{IQ\ =\ 9}$ 0.71, 95% CI 0.63−0.80; $p_{association}$ < .001; $p_{nonlinearity}$ = .274) (Figure 2E).

Lower average IQ scores were observed for fathers of children affected by ASD+ADHD+ID (mean = 4.91) and

Note: Neurodevelopmental disorders were examined as seven mutually exclusive diagnostic outcomes. For each outcome, the top panel displays the distribution of paternal IQ among affected offspring (solid line) compared to the distribution of paternal IQ among offspring not affected by any of the diagnostic outcomes studies here (dashed line). The bottom panel displays the risk of each outcome according to paternal IQ level, flexibly fit using a restricted cubic spline model with five knots and IQ =5 (average intelligence) set as the referent. The dotted line represents the unadjusted estimate of the relationship between each outcome and paternal IQ. The solid line represents the fully adjusted model (adjusted for children's characteristics: sex, birth year, birth order; and for family characteristics: maternal age, paternal age, highest parental education level, family income quintile, maternal migration status, and parental psychiatric history). The gray bands represent the 95% confidence interval for the fully adjusted model. Results are shown for (A) autism spectrum disorder (ASD) without co-occurring intellectual disability/attention-deficit/hyperactivity disorder (ID/ADHD) (ASD only), (B) ASD with co-occurring ID (ASD + ID), (C) ID without ASD/ADHD (ID only), (D) ASD with co-occurring ADHD (ASD + ADHD), (E) ADHD without ASD/ID (ADHD only), (F) ASD with co-occurring ID and ADHD (ASD + ID + ADHD), and (G) ID with co-occurring ADHD (ID + ADHD). OR = odds ratio. Please note color figures are available online.

for fathers of children affected by ID+ADHD (mean = 3.93). Low paternal IQ scores were associated with increased risk for both of these outcomes, although the associations were weaker for ASD+ADHD+ID ($aOR_{IQ=1}$ 2.68, 95% CI 1.81−3.96; $aOR_{IQ=9}$ 0.91, 95% CI 0.59−1.42; $p_{association} < .001$; $p_{nonlinearity} = .021$) (Figure 2F) than for ID+ADHD ($aOR_{IQ=1}$ 5.21, 95% CI 3.79-7.16; $aOR_{IQ=9}$ 0.48, 95% CI 0.24−0.98; $p_{association} < .001$; $p_{nonlinearity} = .025$) (Figure 2G).

When considering the overlapping diagnostic groups, the association of low paternal IQ with any ASD diagnosis ($aOR_{IQ=1}$ 1.33, 95% CI 1.17−1.50) was stronger compared to the association of low paternal IQ with ASD without ID/ADHD (described above), and the association with high paternal IQ was attenuated ($aOR_{IQ=9}$ 1.23, 95% CI 1.10−1.36; $p_{association} < .001$; $p_{nonlinearity} < .001$) (Figure S2A, available online). The association of low paternal IQ with any ID diagnosis was attenuated ($aOR_{IQ=1}$ 3.41, 95% CI 2.95−3.94) compared to the association of paternal IQ with ID without ASD/ADHD, and the protective effect of high paternal IQ was also attenuated ($aOR_{IQ=9}$ 0.91, 95% CI 0.76−1.10; $p_{association} < .001$; $p_{nonlinearity} < .001$) (Figure S2B, available online). The association of low paternal IQ with any ADHD diagnosis was stronger compared to the association of low paternal IQ with ADHD without ASD/ID ($aOR_{IQ=1}$ 1.63, 95% CI 1.50−1.78), and the protective effect of high paternal IQ was attenuated ($aOR_{IQ=9}$ 0.78, 95% CI 0.71−0.86; $p_{association} < .001$; $p_{nonlinearity} < .001$) (Figure S2C, available online).

Of the individual covariates, adjustment for parental education attainment (highest of the mother or father) had the strongest modulating effects on the relationship between paternal IQ and each of the outcomes (Figure S3, available online). In all, 60.30% of the mothers and fathers shared the same education level. Adjusting for maternal or paternal education individually had an effect similar to that of adjustment for parental education attainment (Figure S4, available online).

IQ Subdomain Analysis

Examining paternal scores on individual tests of the enlistment battery (Figure 3), the increased risk of ASD associated with high paternal IQ appears to be driven mainly by the score on the technical comprehension test ($aOR_{Technical\ IQ=9}$ 1.53, 95% CI 1.31−1.78). Scores on the other three tests were not associated with offspring risk of ASD without ID/ADHD ($p_{association} > .05$) (Table S4, available online). The association between low paternal IQ and offspring risk of ASD+ID was most apparent for scores on the spatial ($aOR_{Spatial\ IQ=1}$ 1.70, 95% CI 1.15−2.49) and technical tests ($aOR_{Technical\ IQ=1}$ 2.06, 95% CI 1.49−2.85). Increased risk for ASD+ADHD was most strongly associated with lower paternal scores on the logic ($aOR_{Logic\ IQ=1}$ 1.61, 95% CI 1.32−1.96) and verbal tests ($aOR_{Verbal\ IQ=1}$ 1.49, 95% CI 1.21−1.83). Increased risk of ASD+ADHD was observed for higher paternal scores on the technical test ($aOR_{Technical\ IQ=9}$ 1.43, 95% CI 1.17−1.73). Risk for ASD+ID+ADHD was consistently associated with low paternal scores across all tests. For formal tests of association and nonlinearity for these analyses, see Table S4, available online.

A generally consistent pattern was observed across all tests for the relationship of paternal IQ and offspring risk for ID only, ADHD only, and ID+ADHD (Figure S5, Table S4, available online).

Sex-Stratified Analysis

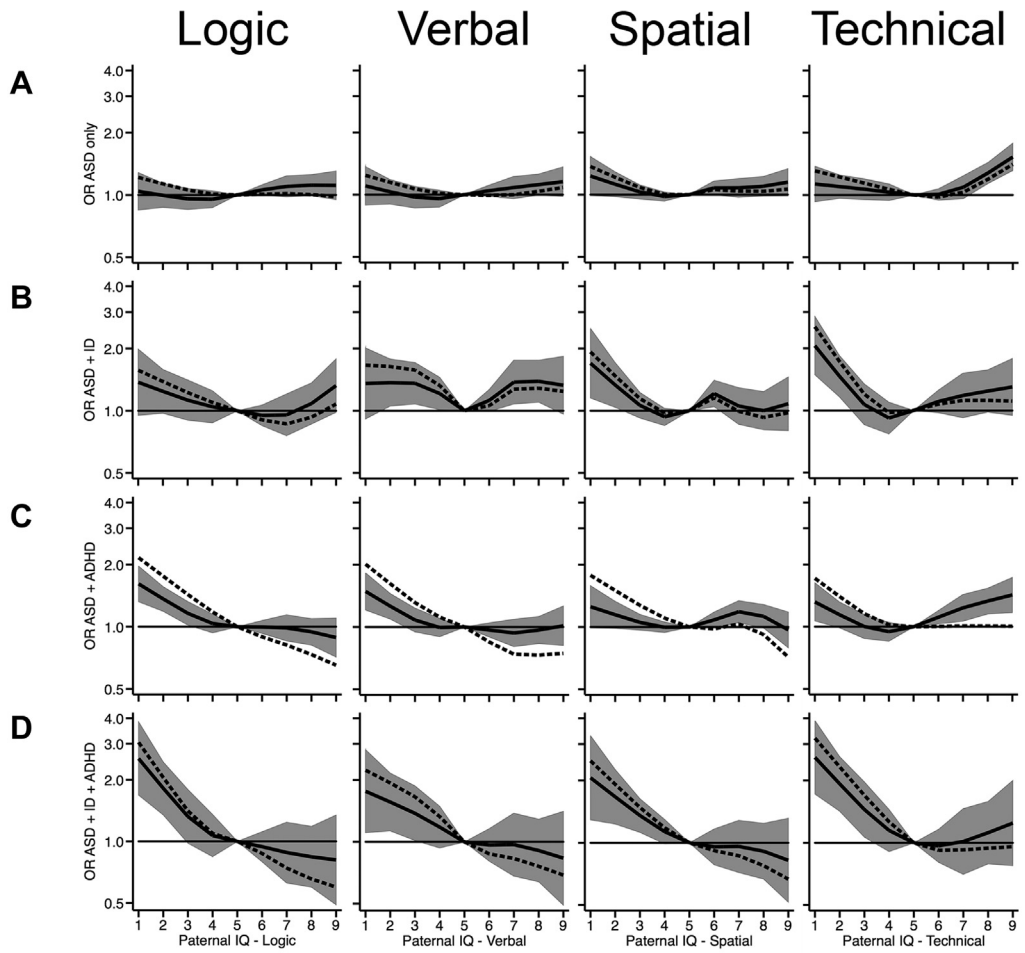
Although male individuals were more likely to be diagnosed with ASD or ADHD at every paternal IQ strata, male and female individuals were about equally likely to be diagnosed with ID (Table S5, available online). Risk of ASD without ID/ADHD associated with above-average paternal IQ was more apparent among male offspring ($aOR_{IQ=9}$ 1.47, 95% CI 1.24−1.73) compared to female offspring ($aOR_{IQ=9}$ 1.04, 95% CI 0.80−1.35) (Figure S6A, available online). Similarly, the increased risk of ASD that associated with high paternal scores only on the technical and logic tests was most apparent among male offspring compared to female offspring (Figure S6A, available online).

An elevated risk of ASD+ID associated with above-average paternal IQ was apparent only among male offspring ($aOR_{IQ=9}$ 1.50, 95% CI 1.09-2.07) (Figure S6B, available online). High paternal scores on the logic and technical comprehension tests were associated with increased risk of ASD+ID only among male offspring (Figure S6B, available online). The associations between low paternal scores and offspring risk of ASD+ID were stronger among female offspring for the verbal and technical tests.

The relationship between low paternal IQ and risk of ASD+ADHD was more apparent among female offspring ($aOR_{IQ=1}$ 2.03, 95% CI 1.44−2.86) compared to male offspring ($aOR_{IQ=1}$ 1.23, 95% CI 0.97−1.54), with a similar pattern observed across all subdomain tests (Figure S6C, available online). In contrast to the results for ASD+ID or ASD only, the risk of ASD+ADHD associated with high paternal IQ scores on the technical test was more apparent among female offspring (Figure S6C, available online).

The risk for ASD+ADHD+ID associated with low paternal IQ was more apparent for male offspring than

FIGURE 3 Relationship Between Paternal IQ and Offspring Risk of Autism Spectrum Disorder According to Scores on Individual Tests of the Swedish Enlistment Battery



Note: Scores were available for a subcohort of 309,803 individuals born to 162,524 fathers. The risk of each outcome according to paternal IQ score on the logic, verbal comprehension, spatial ability, and technical comprehension tests was flexibly fit using a restricted cubic spline model with five knots and IQ = 5 (average intelligence) set as the referent. The dotted line represents the unadjusted estimate of the relationship between each outcome and paternal IQ. The solid line represents the fully adjusted model (adjusted for children's characteristics: sex, birth year, birth order; and for family characteristics: maternal age, paternal age, highest parental education level, family income quintile, maternal migration status, and parental psychiatric history). The gray bands represent the 95% CI for the fully adjusted model. Results are shown for (A) ASD without co-occurring intellectual disability/attention-deficit/hyperactivity disorder (ID/ADHD) (ASD only), (B) ASD with co-occurring ID (ASD + ID), (C) ASD with co-occurring ADHD (ASD + ADHD), (D) ASD with co-occurring ID and ADHD (ASD + ID + ADHD). The relationship between paternal scores on these tests and the diagnoses without ASD are shown in Figure S5, available online. OR = odds ratio.

female offspring across all tests, although the number of individuals, particularly female individuals, in this diagnostic group greatly limited power for this analysis (Figure S6D, available online).

For ID and ADHD diagnoses, stratification of the sample by sex did not substantially alter the risk associated with paternal IQ scores (Figure S7, available online).

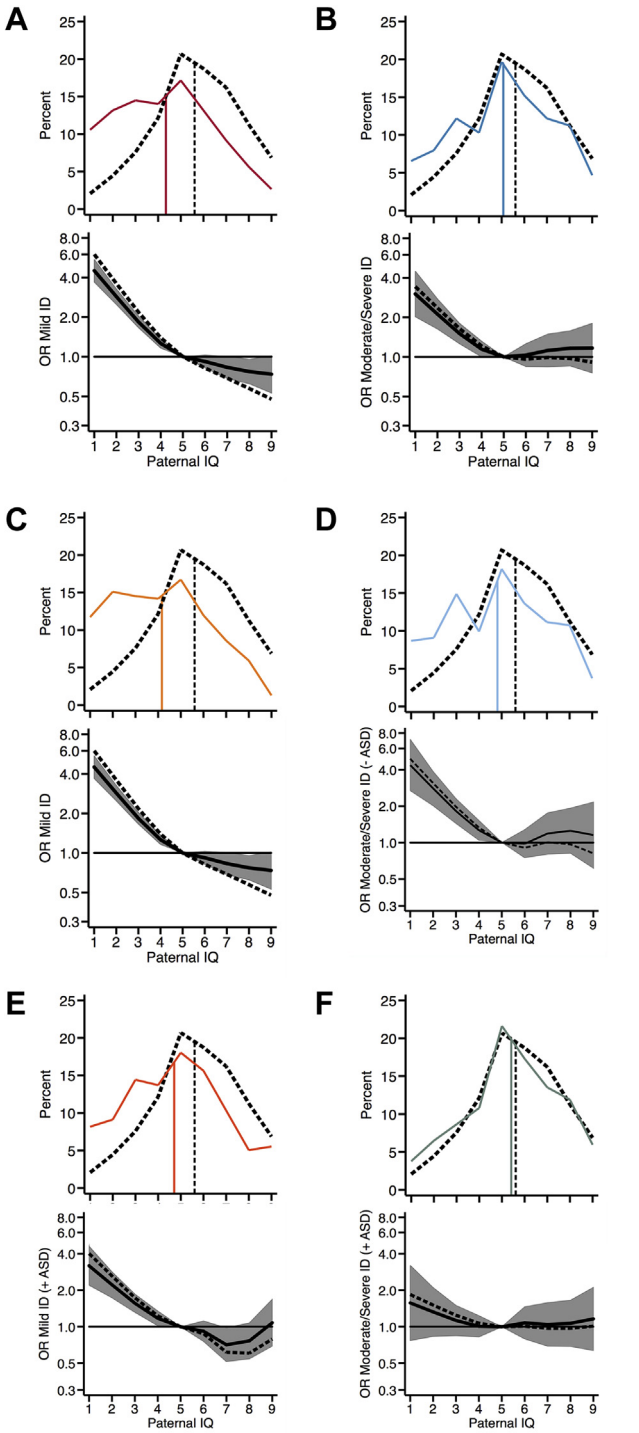
Severity of ID and Paternal IQ

Information on severity was available for 73% of the ID cases in our cohort (Table S6, available online). Fathers of children with mild ID had on average lower IQ (4.34) compared to fathers of children with a diagnosis of moderate (4.90) or severe (5.37) ID (Figure S8, available online; Figure 4). When combined, the mean paternal IQ for the moderate/severe ID group was 5.07 (Figure 4B). Children born to fathers with IQ scores below average were at increased risk for both mild ID ($aOR_{IQ=1}$ 4.51, 95% CI 3.70−5.50) and moderate/severe ID ($aOR_{IQ=1}$ 3.02, 95% CI 2.02−4.50) (Figure 4). Estimates were similar for the moderate and severe ID groups when evaluated separately (Figure S8, available online).

After stratification on the presence of co-occurring ASD, low paternal IQ was associated with mild ID with

ASD ($aOR_{IQ = 1}$ 3.19, 95% CI 2.20−4.61) (Figure 4C), but no relationship was apparent between low paternal IQ and moderate/severe ID with ASD ($aOR_{IQ = 1}$ 1.57, 95 CI = 0.77−3.22) (Figure 4D). In contrast, low paternal IQ increased the odds of both mild ($aOR_{IQ = 1}$ 5.27, 95% CI 4.17−6.66) (Figure 4E) and moderate/severe ID ($aOR_{IQ = 1}$ 4.37, 95% CI 2.68−7.12) (Figure 4F) without co-occurring ASD.

FIGURE 4 Relationship Between Paternal IQ and Offspring Risk of Intellectual Disability (ID), According to ID Severity and Presence of Co-occurring Autism Spectrum Disorder (ASD)



DISCUSSION

This population-based cohort study reports data from more than 300,000 individuals whose fathers were subjected to standardized cognitive testing as part of conscription to the Swedish military. We considered the outcomes of ASD, ADHD, and ID among these individuals. Using fathers with an average IQ score as a referent, we observed a modest association between high paternal IQ scores and risk for ASD (without co-occurring ADHD or ID). When we examined paternal performance on the individual subtests of the enlistment battery, the association of ASD with high paternal IQ was apparent only for the test of technical reasoning. In contrast, low paternal IQ scores were strongly associated with risk of ID (without ASD or ADHD) and were modestly associated with risk of ADHD (without ASD or ID). When ID or ADHD co-occured with ASD, the associations with low paternal IQ were attenuated compared to these outcomes without ASD. Patterns of association varied with the sex of the index person and the severity of ID as an outcome.

The strengths of this study include the large, population-based cohort with prospectively collected data in a setting with universal access to comprehensive health care. Information regarding paternal cognitive scores and children's neurodevelopmental outcomes was collected in national and regional registries that are well established and mandated by law, minimizing the risk of any selection bias. A particular strength of this study is that we were able to

Note: For each outcome, the top panel displays the distribution of paternal IQ among affected offspring (solid line) compared to the distribution of paternal IQ among offspring unaffected by any of the diagnostic outcomes studies here (dashed line). The bottom panel displays the risk of each outcome according to paternal IQ level, flexibly fit using a restricted cubic spline model with five knots and IQ = 5 (average intelligence) set as the referent. The dotted line represents the unadjusted estimate of the relationship between each outcome and paternal IQ. The solid line represents the fully adjusted model (adjusted for children's characteristics: sex, birth year, birth order; and for family characteristics: maternal age, paternal age, highest parental education level, family income quintile, maternal migration status, and parental psychiatric history). Results are shown for (A) any mild ID diagnosis (IQ=50-69), (B) any moderate to severe ID diagnosis (IQ<50), (C) mild ID without ASD, (D) moderate to severe ID without ASD, (E) mild ID with ASD, (F) moderate to severe ID with ASD. For this analysis, the previously described outcomes of ID only and ID with ADHD were grouped (C and D), as were the outcomes of ASD with ID and ASD with ID and ADHD (E and F), due to the small numbers in some groups after stratification by ID level. ADHD = attention-deficit/hyperactivity disorder; ASD = autism spectrum disorders; ID = intellectual disability; OR = odds ratio. Please note color figures are available online.

consider not only ASD but also the commonly co-occurring disorders ID and ADHD. Considering these outcomes, both when they co-occur with ASD and when they occur without ASD, allowed us examine relationships to paternal IQ that were unique to each diagnostic group, and to question whether these relationships changed in comorbid groups. Relationships that were apparent in the mutually exclusive groups were sometimes obscured or attenuated in the analyses that considered overlapping diagnostic groups. For example, an association between low paternal IQ and any ASD diagnosis is apparent, similar to the diagnostic groups ASD with ID and ASD with ADHD but in contrast to ASD without ID/ADHD, whereas the association between high paternal IQ and any ASD diagnosis is attenuated compared to that in the diagnostic group of ASD without ID/ADHD. In addition, we were able to consider different cognitive domains as represented by the subtests that constituted the Swedish Enlistment Battery, thus allowing us to consider specific aspects of paternal cognitive abilities in relation to offspring risk of neurodevelopmental disorders.

Given that parental age is associated with many of the outcomes described here (see Figure S1, available online), and that distribution of paternal age varies over the range of paternal IQ scores, one strength of the study is that all of the fathers included in the study were evaluated at approximately the same age, regardless of their age when they became fathers.

The limitations of this study relate primarily to the availability of IQ data for fathers, as only male individuals were conscripted. As such, it was not possible to look at the relationships between maternal IQ and offspring risk of neurodevelopmental disorders, nor was it possible to examine the joint effects of maternal and paternal cognitive performance on these outcomes, although we would expect the influence of maternal factors to be at least as great as the paternal factors. It should be noted that immigrants to Sweden were largely not conscripted. Thus, children of immigrants are underrepresented in this sample. Previous work has shown that children of immigrants to Sweden have different prevalences of certain neurodevelopmental disorders compared to children of Swedish-born parents.[32,33] Although the exclusion of such families potentially limits the generalizability of our study, including non−native Swedish speakers in the cognitive assessment might, have made the results less reliable, because these men would be at a disadvantage compared to native speakers on a cognitive test given in Swedish. Some men with psychiatric disorders were also exempt from military conscription, as were men with clinically apparent ID, leading to an underrepresentation of fathers with severe mental illness and ID.

A further limitation relates to the validation of the outcomes. The procedures for validating ASD and ADHD diagnoses were different and have been carried out by different research groups. The positive predictive value for ASD diagnoses was 96% in validation studies comparing registered diagnoses to a review of clinical records.[27] Validation of ADHD diagnoses, carried out by comparing parental questionnaires to register diagnoses for a cohort of twins, estimated a 70% positive predictive value for the register diagnoses, making the register-based outcome of ADHD potentially less reliable compared to ASD.[26] Although the IQ estimates supporting the diagnoses for ID can be considered as a validation of the diagnosis, 27% of the individuals with an ID diagnosis received a diagnosis that included no information regarding the IQ estimate (see Table S6, available online), as they were coded as "unspecified" ID or were categorized as having ID by habilitation registers that record the presence or absence of ID (see Table S2, available online), and thus these diagnoses of ID may be considered as potentially less reliable.

Considering the familial basis of cognitive abilities and neurodevelopmental disorders, previous large-scale, population-based studies have examined cognitive abilities as an outcome among those with a first-degree relative diagnosed with ASD, ID, or ADHD. In the only study to date regarding ASD, male individuals diagnosed with ASD tended to score lower on cognitive tests compared to those with no psychiatric history, whereas men whose siblings were diagnosed with ASD scored higher compared to siblings of unaffected individuals, in a population of young men conscripted to the Danish military.[34] The same study showed lower IQ scores among the male conscripts with a sibling with a diagnosis of ID and among those with a sibling with a childhood-onset behavioral or emotional disorder (ICD10: F90-98, a category that includes F90 ADHD). A similar study of military conscripts in Sweden and Israel showed that the IQ of siblings to individuals with mild ID (defined in that study as the lowest score of one on the stanine scale) tended to have lower IQ, whereas individuals whose siblings had received a register-based diagnosis of severe ID had a distribution of IQ similar to that in the general population.[20] The distributions of IQ among siblings in that study are highly comparable to the distributions observed among the fathers of children with mild and severe ID in our study.

Our observation that risk of ASD increases with above-average paternal IQ scores suggests that intelligence is associated with ASD not only genetically but also phenotypically.[8,9,22,34] This observation is in agreement not only with a recent Mendelian randomization study[12] but also with the original case reports of autism.[1,2] We find the

consistency between our observations and the original case reports to be remarkable, given both the diagnostic changes that have occurred in the field, as well as the social patterning in Sweden, where ASD is more prevalent among those of lower socioeconomic status.[7] The association appeared to be driven by scores on the technical comprehension subtest, in agreement with observational studies regarding a slight excess of parents to ASD probands working within technical professions[4,6] and adding support to a recently articulated medical hypothesis that ASD etiology often "involves enhanced, but imbalanced, components of intelligence."[14]

The relationships between paternal IQ and offspring risk of ASD diagnoses were not monotonic, and, for ASD with co-occurring ID and/or ADHD, we also observed an association with low paternal IQ. However, these associations were weaker than the relationships between paternal IQ and the outcomes of ID and/or ADHD without co-occurring ASD, probably reflecting the phenotypic and etiologic diversity among ASD-affected individuals with or without other co-morbid conditions in our sample.

The modest inverse association that we observed between paternal cognitive performance and ADHD risk in the offspring, consistent across the different subtests and with no major influence of offspring sex, is in agreement with recent studies reporting inverse genetic associations between cognitive abilities and ADHD, which Mendelian randomization studies argue are causal.[10,12,35]

We observed a strong association between low paternal IQ and diagnosed ID in the offspring, consistent across subtests and sex of the offspring. This finding is perhaps not surprising, given the fairly high heritability of IQ.[36] The association between low paternal IQ became progressively weaker by increasing severity of ID, similar to findings regarding the IQ of siblings of mildly versus severely affected individuals with ID.[20] Somewhat to our surprise, risk for ID associated with low paternal IQ remained even for severe ID. Although noninherited environmental (eg, lead exposure[37]) or genetic (eg, *de novo* mutations[38]) insults can impair cognitive function, parental cognitive abilities have been reported to still influence variation in the cognitive performance of the affected individuals.[38] Offspring with lower inherited cognitive abilities would therefore be more likely to fall below any clinical cut-off drawn to connote severity of ID (ie, <70 or <50) following such insults. The relationship between paternal IQ and offspring risk for ID varied by the presence of co-occurring ASD such that no relation was observed between paternal IQ and risk for ASD with co-occurring moderate/severe ID. These observations in a population-based study support the notion that the origins of ID in ASD may differ from those of ID without ASD.

Assuming that the association between paternal IQ and offspring risk of neurodevelopmental disorders is largely due to common genetic variation,[8-12] our findings regarding a stronger relationship between high paternal IQ and offspring risk of ASD among male offspring are in line with the notion that female individuals are somewhat protected from familial risk of ASD.[39,40] However, the stronger associations between paternal IQ scores and risk of ASD+ADHD among female offspring would not support this theory. Although the sex ratio observed in our population-based sample is substantially lower than the frequently estimated 4:1 sex ratio for ASD,[41] bias in ASD ascertainment in this sample may also occur. Female individuals (particularly those of higher cognitive abilities) may be less likely to be diagnosed with ASD, perhaps because of a greater ability to compensate for symptoms of the disorder compared to male individuals.[42] In molecular genetic studies, alleles associated with ASD and with educational attainment (a proxy for cognitive abilities) were reported to be transmitted equally to affected offspring of both sexes,[22] suggesting that there is no sex bias in terms of transmission of common alleles associated with ASD or cognition. Taken together, these observations suggest that our results regarding differences in risk among the sexes should be interpreted with caution, as they may reflect diagnostic tendencies rather than etiological differences.

Overall, the relationship between paternal IQ and offspring risk of neurodevelopmental disorders were attenuated toward the null after adjustment by potentially confounding factors, with the exception of the associations between above-average paternal IQ and ASD only and ASD+ID, which were somewhat strengthened after adjustment, similar to the observations of McGrath *et al.*[34] As educational attainment is associated with IQ and could be considered a proxy for IQ,[9,12,43] adjustment for parental educational attainment may result in overadjustment of the model. However, Mendelian randomization studies suggest that educational attainment causally influences IQ.[12] We have therefore presented both unadjusted and adjusted model estimates, which lead to the same conclusions regarding the direction of associations between paternal IQ and offspring risk of neurodevelopmental disorders.

In our study, the relationships between paternal IQ and offspring risk of ASD varied by the presence of co-occurring disorders and were not monotonic, reflecting the phenotypic diversity among ASD-affected individuals. High scores on a test of technical understanding capture a familial component of ASD risk and may, to some extent, explain the clinical and anecdotal observations historically made regarding career choices among parents of autistic children. In contrast, factors associated with low general cognitive

ability capture some of the familial risk for ADHD and for ID. The ID diagnosed in individuals with ASD, however, appears to be less heritable and may therefore have other causes compared to ID without ASD.

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Data Sharing: The Swedish health and population register data used in this study are available from Statistics Sweden (https://www.scb.se/en/) and the Swedish National Board of Health and Welfare (https://www.socialstyrelsen.se/en/about-us/). The authors are not allowed to distribute the data according to the ethical approval for this study and the agreements with Statistics Sweden and the Swedish National Board of Health and Welfare.

Christina Dalman and Renee Gardner had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Renee Gardner and Håkan Karlsson conceived the study. Renee Gardner and Håkan Karlsson conducted the literature search. Renee Gardner conducted and is responsible for the data analysis. All authors contributed to the planning of the study and interpretation of statistical analyses. Renee Gardner and Håkan Karlsson drafted the manuscript, and all authors have read and critically revised the manuscript.

Dr. Gardner served as the statistical expert for this research.

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